

REMARKS

Claims 1, 2, 5, 9 and 10 have been amended to specify that the ELN +/- mouse has increased number of elastic lamellae and that the ELN -/- mouse has arterial occlusion. The Examiner has stated that these phenotypes for these mice are enabled by the specification. Claim 6 has been canceled. It is submitted that these amendments do not constitute new matter, and their entry is requested.

The Examiner rejected claim 6 under 35 U.S.C. § 112, first paragraph for lack of enablement. The cancellation of claim 6 obviates this rejection, and its withdrawal is requested.

The Examiner rejected claims 1, 2, 5, 9 and 10 under 35 U.S.C. § 112, first paragraph for lack of enablement. It is believed that the amendment of claims 1, 2, 5, 9 and 10 to set forth the enabled phenotype for each genotype obviates the rejection with respect to these claims. Withdrawal of this rejection is requested.

The Examiner rejected claims 3-4 under 35 U.S.C. § 103 as being unpatentable over Sechler et al. (1995) in view of Morris (1998) and Wydner et al. (1994). Applicants submit that the present invention was made prior to the publication date of the Morris reference. Therefore, Applicants submit that Morris is not prior art with respect to the present invention. Applicants submit herewith a Rule 131 Declaration swearing behind the Morris reference. This declaration establishes that the present invention was made at least prior to May 1998, the date of the Morris reference.

Since Morris is not prior art with respect to the present invention, Applicants submit that the presently claimed invention is not obvious over Sechler et al. in view of Wydner et al. for the reasons previously provided. Specifically, Applicants urge that at best the combination of the cited references would motivate one of skill in the art to make mice which are transgenic for a mutated mouse elastin gene but which also comprise normal wild-type mouse elastin genes. The mice of the Sechler et al. reference comprise not only the transgenic mutant rat elastin gene but also comprise the normal wild-type mouse elastin genes which are still active. This is seen in several places in the reference. The first paragraph of the Results and discussion section on page 150 of the Sechler et al. reference states that the reasoning behind the construction of the mice was to produce mice which would synthesize a mutated elastin which would be incorporated into the elastin matrix together with the normal, endogenous mouse elastin. This clearly establishes the motivation of producing the mice

- to study animals making a combination of both mutant and wild-type elastin. Data showing that the mice studied for the publication did in fact produce both types of elastin is shown, e.g., in Table 1 on page 153 of the Sechler et al. publication. Both rat and mouse tropoelastin mRNA were produced with the levels of endogenous mouse tropoelastin mRNA set at a value of 100% and the rat levels based on a comparison to that value. The middle of the last paragraph on page 14 of the publication states that levels of expression of the rat transgenes in skin was usually comparable to or exceeded that of the endogenous expression of the mouse gene. Table 2 on page 158 of the Sechler et al. publication shows that both the rat and mouse elastin proteins were being synthesized in the transgenic animals.

The claims which are pending are not drawn to mice or mouse cells comprising a **mutated** gene plus a wild-type gene, rather the claims are drawn to mice or cells which have a) a single functional elastin gene or ii) no elastin gene. This difference is critical. The claimed mice and cells are ones which end up being **deficient** in elastin rather than comprising some type of **mutated** elastin. Mice (and humans) which are deficient in elastin have different medical conditions than those which synthesize a mutated elastin.


It is submitted that the present claims do not encompass elastin genes which are transcribed but are nonfunctional because of a mutation which is present, rather they encompass the presence of only at most a single elastin gene which produces an elastin protein which can be incorporated into a matrix. It is urged that the claim language clearly distinguishes the claims from the prior art and prevents the claims from being read broadly enough to be encompassed by or made obvious by the prior art. No prior art reference has been cited that teaches a mouse or mouse cell comprising no or only one elastin gene, which will be transcribed into RNA that will be translated into a protein which can be incorporated into the extracellular matrix.

Applicants urge that there is a crucial difference between the prior art and the claimed invention. The prior art teaches medical problems which are associated with the presence of a **mutated** elastin, not with a **deficiency** of elastin. The Sechler et al. reference teaches on pages 162-163 that disruptions in the region of the elastin gene are associated with SVAS. In fact, this teaching states that it was not known if the disruption of the elastin gene causes the SVAS phenotype or whether the defect results from a disruption of another gene near the elastin gene (see the final

sentence on page 162 continuing onto page 163). Based on this fact alone, it is urged that at best there would be merely an "obvious to try" motivation to produce mice with mutated elastin genes and the usefulness of such mice would not be "obvious". This alone should be enough to overcome the "obviousness" rejection. However, applicants urge that there are even more reasons that the obviousness rejection is improper. If one were to accept that the references teach that mutations in elastin actually do result in SVAS, the Sechler et al. reference teaches that these mutations involve a breakpoint near the 3' end of the tropoelastin gene (see the final paragraph on page 162). This means that a somewhat truncated version of elastin is produced and it is this truncated version which causes SVAS. The Sechler et al. reference teaches that there is support for the idea that incorporation of the truncated elastin into fibers results in SVAS (see page 163). Therefore to study SVAS one would be motivated to produce mutated elastin such that a mutant form of elastin would be produced and be inserted into fibers to produce aberrant fibers. That is exactly what Sechler et al. did and that is what their results support, i.e., they prepared mice which produced mutated forms of elastin. Sechler et al. produced no mice which were deficient in elastin, rather their mice produced normal amounts of wild-type elastin plus a mutated form of elastin which interacted with wild-type elastin in forming aberrant fibers and produced mice which have fiber morphology similar to SVAS (see page 163). These results would point one in the direction of studying mutated forms of elastin rather than gene dosage effects. It is urged that no references have been pointed to which disclose any studies on mice which are deficient in elastin, rather the prior art teaches that conditions such as SVAS are likely caused by mutated forms of elastin being incorporated into fibers thereby producing aberrant fibers. This would not lead one to conclude that a mouse producing a deficient amount of solely wild-type elastin would produce aberrant fibers since only wild-type elastin would be present. The results disclosed in the present application teach otherwise, but such studies were never reported in the prior art. The medical condition which results from a lack of elastin is different from that seen due to the presence of a mutated elastin. Mutated elastin leads to aberrant elastic fibers whereas a lack of elastin results in proliferation of smooth muscle and contributes to obstructive arterial disease (see Summary of the Invention on pages 2-3 of the application). It is urged that the prior art would lead one only to study mice with mutated forms of elastin, not to study mice with solely a deficiency of wild-type elastin.

In view of the above remarks, it is believed that claims 3-4 are not rendered obvious by the cited prior art. Withdrawal of this rejection is requested.

In view of the amendments and above arguments, it is submitted that the present claims satisfy the provisions of the patent statutes and are patentable over the prior art. Reconsideration of this application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned to expedite allowance of this application.

RESPECTFULLY SUBMITTED,					
<i>Name and Reg. Number</i>	Jeffrey L. Ihnen, Reg. No. 28,957				
<i>Signature</i>				<i>Date</i>	3 September 2002
<i>Address</i>	Rothwell, Figg, Ernst & Manbeck 1425 K Street, N.W., Suite 800				
<i>City</i>	Washington	<i>State</i>	D.C.	<i>Zip Code</i>	20005
<i>Country</i>	U.S.A.	<i>Telephone</i>	202-783-6040	<i>Fax</i>	202-783-6031

Attachments: Marked-Up Copy of Amendments
Declaration Under 37 C.F.R. 1.131

Amended Claims: Version with markings to show changes made

1 (five times amended). A mouse comprising a genome comprising a) exactly one functional elastin gene and b) either one mouse elastin gene comprising a null mutation or no second elastin gene, wherein said mouse has an increased number of elastic lamellae ~~and arterial occlusion~~.

2 (twice amended). A mouse comprising a genome with no functional elastin gene, wherein said mouse has ~~an increased number of elastic lamellae~~ and arterial occlusion.

5 (four times amended). A method to screen for drug candidates useful for treating humans with SVAS, hypertension or atherosclerosis or useful for preventing atherosclerosis in humans, said method comprising administering said drugs to an *ELN* +/- mouse or human, wherein said *ELN* +/- mouse or human comprises a genome with a) exactly one functional elastin gene and b) either one elastin gene comprising a null mutation or no second elastin gene, wherein said mouse has an increased number of elastic lamellae ~~and arterial occlusion~~, wherein drugs which inhibit occlusion of arteries in said organism are said drug candidates.

9 (four times amended). A method to screen for a drug candidate useful for treating atherosclerosis, hypertension or SVAS in a human, said method comprising treating an *ELN* +/- mouse or human or *ELN* +/- mouse or human cells, wherein said *ELN* +/- mouse or human or mouse or human cells comprise a genome with a) exactly one functional elastin gene and b) either one elastin gene comprising a null mutation or no second elastin gene, wherein said mouse has an increased number of elastic lamellae ~~and arterial occlusion~~, with drugs and measuring synthesis of elastin RNA wherein a drug which increases synthesis of elastin RNA in said organisms or in said cells is said drug candidate.

10 (three times amended). A method to screen for a drug candidate useful for treating atherosclerosis, hypertension or SVAS in a human, said method comprising treating *ELN* +/- mice or *ELN* +/- mouse cells, wherein said *ELN* +/- mice or mouse cells comprise a genome with a)

exactly one functional elastin gene and b) either one elastin gene comprising a null mutation or no second elastin gene, wherein said mouse has an increased number of elastic lamellae ~~and arterial occlusion~~, with drugs and measuring synthesis of elastin wherein a drug which increases synthesis of elastin is said drug candidate.